Remarks

Claims 34, 73, 74 and 99-112 are pending herein. By this Amendment, 33, 36, 38, 40-72 and 75-97 have been canceled; claims 34, 73 and 74 have been amended; and new claims 99-112 have been added.

Claim 34 has been amended to depend upon new claim 99 rather than canceled claim 33.

Claim 73 has been amended to limit the disease therein to myocardial infarcts, myocardial perfusion, and cancer. Claim 73 has been further amended to depend upon new claim 99.

Claim 74 has been amended to limit the disease therein to cancer, and to depend upon new claim 99.

Independent claim 33 has been replaced by new independent claim 99. Specifically, claim 99 combines the features of canceled claims 33, 36, 38, 40-42, 59, 66, and 67; and withdrawn claims 44, 48, 60, 61, 68 and 69.

Support for new claim 100 can be found, e.g., in the specification at page 1, line 26.

Support for new claim 101 can be found, e.g., in the specification at page 10, lines 6-7.

Support for new claim 102 can be found, e.g., in the specification at page 6, lines 9-10.

Support for new claim 103 can be found, e.g., in withdrawn claim 48.

Support for new claim 104 can be found, e.g., in the specification at page 13.

Support for new claim 105 can be found, e.g., in withdrawn claim 50.

Support for new claim 106 can be found, e.g., in withdrawn claim 51.

Support for new claim 107 can be found, e.g., in withdrawn claims 46 and 47.

Support for new claim 108 can be found, e.g., in canceled claim 33.

Support for new claim 109 can be found, e.g., in canceled claims 55 and 64.

Support for new claim 110 can be found, e.g., in canceled claims 56 and 65.

Support for new claim 111 can be found, e.g., in canceled claim 62.

Support for new claim 112 can be found, e.g., in cancelled claim 70.

In the Office Action, claims 73 and 74 are rejected under 35 U.S.C. §112, first paragraph; claims 33, 34, 40, 41, 55-59, 62, 64-67, 70, 73, 74, 88 and 89 are rejected under 35 U.S.C. §103(a) as being unpatentable over WO 97/29114 to Wilbur et al. ("Wilbur") in view of Rosebrough, The Journal of Pharmacology and Experimental Therapeutics, vol. 265, No. 1, 1993, 408-415 ("Rosebrough"); claims 36 and 38 are rejected under 35 U.S.C. §103(a) as being unpatentable over Wilbur and Rosebrough and further in view of U.S. Patent No. 5,482,698 to Griffiths ("Griffiths"); and claims 33, 34, 36, 38, 55-59, 62, 64-67, 70, 73, 74, 88 and 89 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10, 17-19 and 21-23 of copending Application No. 09/519,998 ("the '998 application").

In view of the amendments and remarks herein, Applicant respectfully requests reconsideration and withdrawal of the rejections set forth in the Office Action.

I. Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 73 and 74 are rejected under 112, first paragraph, because the specification, while enabling for diagnosis of myocardial infraction and certain cancers and treatment of certain cancers, is said to not reasonably provide enablement for diagnosis and treatment of any condition or disease in a mammal.

Claim 73 has been amended to limit the disease therein to myocardial infarcts, myocardial perfusion, and cancer. Claim 74 has been amended to limit the disease therein to cancer.

In view of the amendments to claims 73 and 74, Applicant respectfully requests withdrawal of the §112 rejection.

II. Rejection Under 35 U.S.C. §103(a) Based on Wilbur in view of Rosebrough

Claims 33, 34, 40, 41, 55-59, 62, 64-67, 70, 73, 74, 88 and 89 are rejected under 35 U.S.C. §103(a) as being unpatentable over Wilbur in view of Rosebrough. As stated previously, by this Amendment, claims 33, 36, 38, 40-72 and 75-97 have been canceled. Claims 34, 73, 74 and 99-112 are pending.

Applicant respectfully submits that claims 34, 73, 74 and 99-112 are patentable over Wilbur in view of Rosebrough.

New claim 99 is the sole independent claim. Claim 99 is directed to a single molecule reagent for conjugation to a biomolecule, with minimal perturbation of the biomolecule. The reagent includes an effector agent selected from the group consisting of radionuclide binding/bonding moieties. The moieties are bound via chelation to amino-carboxy derivatives or cyclic amines, and the amino-carboxy derivatives or cyclic amines are coupled to "X" in structure (I) via a linker 2. Furthermore, the linker 1 in the reagent of claim 99 has a length of at least 9 angstroms.

In the claimed invention, because the effector agents are bound via chelation to amino-carboxy derivatives or cyclic amines, the radionuclides become tightly bound to the reagent and will not become separated from the biotinylated part during use of the reagent. As a result, the possibility that "non-conjugated" radionuclides could circulate within the blood of the patient which has been treated with the reagent is eliminated, and all the reagents which have not been bound to the target cells can efficiently be removed from the blood system.

Another improvement provided by the claimed invention is that by ensuring that the radionuclide remains bound to the reagent, there is no possibility that reagents without radionuclides will bind to the target within the patient to be treated and occupy the target, so that no reagent with a radionuclide or a lower amount of reagent with a radionuclide can be bound. Thus, with the present invention, the effect of the treatment is secured.

Furthermore, having a linker 1 with a length of at least 9 angstroms in the claimed invention ensures that the biotin is separate from the rest of the reagent, so that it is possible to bind biotin to avidin in a device when surplus reagent is to be removed from the patient, i.e., steric hindrance is eliminated.

Neither Wilbur nor Rosebrough teaches or suggests that binding a radionuclide via chelation to linker 2 to a general structure (I) in claim 99 results in a more stable reagent, wherein the biotin is separated from the rest of the reagent through a linker 1 having a length of at least 9 angstroms. For example, Wilbur mentions different radionuclides that can be used, but nothing about chelation. Rosebrough teaches binding radionuclides through chelating directly to a biotin, and then binding the biotin to a streptavidin to which an antibody has been bound, thereby making it possible to direct the radionuclide to a target within the patient. The object in Rosebrough was to study the stability of the complex *in vivo*. Applicant submits that one skilled

in the art would not have been motivated by Rosebrough to couple the radionuclide directly to a biotin through a linker 2 to the phenolic group of structure (I), which would not be possible to remove from the patient.

Thus, for at least the foregoing reasons, Applicant submits that claim 99 and the claims depending directly or indirectly thereon, i.e., claims 34, 73, 74 and 100-112, would not have been obvious over Wilbur in view of Rosebrough.

III. Rejection Under 35 U.S.C. 103(a) Based on Wilbur and Rosebrough in view of Griffiths

Claims 36 and 38 are rejected under 103(a) as being unpatentable over Wilbur and Rosebrough in view of Griffiths.

Claims 36 and 38 have been canceled, and their contents incorporated into new claim 99. Applicant respectfully submits that claim 99 is patentable over Wilbur and Rosebrough in view of Griffiths.

For the reasons set forth above, Applicant submits that claim 99 is patentable over Wilbur and Rosebrough. Griffiths does not cure the failure of Wilbur and Rosebrough to teach or suggest the invention of claim 99. For example, Griffiths does not teach or suggest anything about chelation or about a specific length for linker 1.

IV. Double Patenting Rejection

Claims 33, 34, 36, 38, 55-59, 62, 64-67, 70, 73, 74, 88 and 89 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10, 17-19 and 21-23 of the '998 application.

On July 28, 2005, Applicant filed a continuation application of the '998 application, which was assigned serial no. 11/190,955. The continuation application was filed with a Preliminary Amendment, a copy of which is enclosed. As shown in the Preliminary Amendment, all of the claims of the continuation are directed to a method of manufacturing a conjugate. Claim 31 (the sole independent claim) recites a method comprising: a) providing a trifunctional cross-linking moiety, a linker 1, a linker 2, a linker 3, an affinity ligand, an effector and a biomolecule reactive moiety; b) coupling the effector agent via linker 2, the affinity ligand via linker 1 and the biomolecule reactive moiety via linker 3 to the trifunctional crosslinking moiety and obtaining a complex; and c) conjugating the complex to a biomolecule via the

biomolecule reactive moiety and obtaining a conjugate, wherein step b) is always prior to step c). Applicant submits that instant claims 34, 73, 74 and 99-112, which are directed to a single molecule reagent for conjugation to a biomolecule, would not have been obvious over the claims of the continuation application.

V. Conclusion

In view of the amendments and remarks herein, Applicant respectfully requests that the rejections set forth in the Office Action be withdrawn and that claims 34, 73, 74 and 99-112 be allowed.

If any additional fees under 37 C. F. R. §§ 1.16 or 1.17 are due in connection with this filing, please charge the fees to Deposit Account No. 02-4300, Order No. 033700.005.

Respectfully submitted,
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Dated: December 13, 2005

Enclosures: (1) Request for Continued Examination
(2) Petition for Extension of Time (Two Months)
(3) Check for the sum of $620
(4) Attachment: Copy of Preliminary Amendment Filed For U.S. Serial No. 11/190,955

LISTING OF CLAIMS

Claims 1-33 (canceled)

Claim 34 (Currently Amended): The single molecule reagent according to claim ~~33~~ 99, wherein the ~~trifunctional cross-linking moiety~~ reagent comprises a member selected from the group consisting of triaminobenzene, tricarboxybenzene, dicarboxyaniline and diaminobenzoic acid.

Claims 35-72 (Canceled)

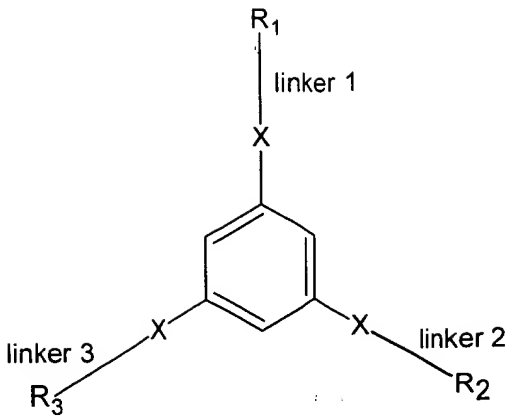
Claim 73 (Currently Amended): A reagent for the diagnosis of a ~~condition or~~ disease in a mammal, the disease being selected from the group consisting of myocardial infarcts, myocardial perfusion, and cancer, and the reagent comprising the single molecule reagent according to claim ~~33~~ 99.

Claim 74 (Currently Amended): A reagent for the treatment of a ~~condition or~~ cancer disease in a mammal, the reagent comprising the single molecule reagent according to claim ~~33~~ 99.

Claims 75-98 (Canceled)

Claim 99 (New): A single molecule reagent for conjugation to a biomolecule with minimal perturbation of said biomolecule, comprising the general structure (I)

(I)



wherein each X is an amino or carboxylic residue;

wherein R_1 is an affinity ligand selected from the group consisting of biotin, norbiotin, homobiotin, oxybiotin, iminobiotin, desthiobiotin, diaminobiotin, biotin sulfoxide, and biotin sulfone having an affinity constant of at least 10^6 M^- to avidin or streptavidin, and is coupled to X in structure (I) via a linker 1;

wherein linker 1 is selected from the group consisting of ethers, thioethers, and ionizable groups comprising carboxylates, sulfonates or ammonium groups, and has a length of at least 9 angstroms;

wherein R_2 is an effector agent selected from the group consisting of radionuclide binding/bonding moieties which are bound via chelation to amino-carboxy derivatives or cyclic amines, said amino-carboxy derivatives or cyclic amines being coupled to X in structure (I) via a linker 2;

wherein linker 2 is selected from the group consisting of ethers, thioethers, and ionizable groups comprising carboxylates, sulfonates or ammonium groups;

wherein R_3 is a biomolecule reactive moiety selected from the group consisting of activated esters, aryl imidates, alkyl imidates, alkyl isocyanates, aryl isocyanates, alkyl isothiocyanates, aryl isothiocyanates, maleimides, alpha-haloamides, aryl hydrazines, alkyl hydrazines, aryl acylhydrazines, alkyl acylhydrazines, alkyl hydroxylamines, and aryl hydroxylamines; said biomolecule reactive moiety being coupled to X in structure (I) optionally via a linker 3;

wherein linker 3 is selected from the group consisting of ethers, thioethers, and ionizable groups comprising carboxylates, sulfonates and ammonium groups.

Claim 100 (New): The single molecule reagent according to claim 99, wherein the biomolecule is a protein or a peptide.

Claim 101 (New): The single molecule reagent according to claim 100, wherein the protein is a monoclonal antibody.

Claim 102 (New): The single molecule reagent according to claim 101, wherein the monoclonal antibody is a tumor binding monoclonal antibody.

Claim 103 (New): The single molecule reagent according to claim 99, wherein R_2 is selected from the group consisting of positron imaging radionuclides, gamma imaging radionuclides and therapeutic radionuclides.

Claim 104 (New): The single molecule reagent according to claim 103, wherein the radionuclide is selected from the group consisting of In radionuclides, Y radionuclides, Pb radionuclides, Bi radionuclides, Cu radionuclides, Sm radionuclides and Lu radionuclides.

Claim 105 (New): The single molecule reagent according to claim 103, wherein the therapeutic radionuclide is selected from the group consisting of Y-90, In-114m, Re-186, Re-188, Cu-67, Sm-157, Lu-177, Bi-212, Bi-213, At-211, and Ra-223.

Claim 106 (New): The single molecule reagent according to claim 103, wherein the gamma imaging radionuclides are Tc-99m or In-111.

Claim 107 (New): The single molecule reagent according to claim 103, wherein R_2 is a DTPA derivative selected from the group consisting of Me-DPTA, CITC-DTPA and cyclohexyl-

DTPA, or a cyclic amine selected from the group consisting of NOTA, DOTA and TETA, for In, Y, Pb, Bi, Cu, Sm and Lu radionuclides.

Claim 108 (New): The single molecule reagent according to claim 99, wherein linker 1 comprises an aspartyl group.

Claim 109 (New): The single molecule reagent according to claim 99, wherein linker 2 and/or linker 3 provides a spacer length of 1 to 25 atoms.

Claim 110 (New): The single molecule reagent according to claim 109, wherein linker 2 and/or linker 3 provides a spacer length of 6 to 18 atoms.

Claim 111 (New): The single molecule reagent according to claim 99, wherein the activated esters are selected from the group consisting of N-hydroxysuccinimide esters, sulfo-N-hydroxysuccinimide esters and phenolic esters.

Claim 112 (New): The single molecule reagent according to claim 99, wherein the reagent is selected from the group consisting of: